Allergy Abstracts

EDITOR
MURRAY M. ALBERT
Brooklyn, N. Y.

ASSOCIATE EDITOR
EUGENE H. WALZER
Bridgeport, Conn.

EDITORIAL BOARD

MONROE COLEMAN
Stamford, Conn.
HAROLD J. FRIEDMAN
Cleveland, Ohio
KATHERINE L. BOWMAN
Brooklyn, N. Y.
HILDA STRYKER
Brooklyn, N. Y.
ELOISE KAILIN
Washington, D. C.
BERNARD B. SIEGEL
Far Rockaway, N. Y.
RICHARD D. WISEMAN
Syracuse, N. Y.
DAVID STEIN
Bethesda, Md.

ASSISTANT EDITORS

I TSU CHAO
Formosa, China
ISRAEL GLAZER
Tel Aviv, Israel
JOSE LUIS CORTES
Mexico, D. F.

CONSULTANT EDITOR

MATTHEW WALZER
Brooklyn, N. Y.

ADVISORY EDITOR

MAX GROLNICK
Brooklyn, N. Y.

FROM THE ALLERGY DIVISION OF THE JEWISH HOSPITAL OF BROOKLYN

Volume 26, Number 1 *January—February, 1961*

ASTHMA AND HAY FEVER

The Electroencephalogram in Migraine and Asthma. Panzani, R., Boyer, R., and Turner, M.: Ann. Allergy **18**: 491, 1960.

Electroencephalograms were studied in 154 cases of headache ("migraine") for which no organic cause could be demonstrated. Of these, 138 were adults (87 women and 51 men). Eighty of the adults complained only of headache, 16 had associated visual phenomena, and 32 also had aphasia or sensory disturbances. Of the 154 patients, only 49 showed normal alpha rhythm. Four had epilepsy. The various dysrhythmias seen are described. The abnormal findings are four times the number found in a random sample of the population. The EEG abnormalities were often localized. It is suggested that small vascular abnormalities in the brain may predispose the patient to migraine.

Of 140 asthmatic adults, 44 were found to have normal tracings, 88 had minor abnormalities, and 8 had major epileptic type abnormalities. The abnormalities were generalized rather than localized. Seven adults had a history of epilepsy. Of 100 asthmatic children, 40 showed normal tracings, 42 had minor abnormalities, and 18 had major abnormalities. Eleven children gave a history of epilepsy and 8 had suffered from convulsions.

Since only four cases of psychomotor epilepsy were observed in 240 cases of asthma, the findings did not suggest a special association between the two conditions. It is suggested that coexistent asthma and epilepsy may aggravate each other and that occasionally EEG abnormalities may be a result of repeated asthmatic or migrainous attacks. The theory that a mesodiencephalic factor may be part of the migraine and especially of asthma is supported by these studies. E. K.

Intermittent Positive-Pressure Respiration and Therapeutic Bronchial Lavage in Intractable Status Asthmaticus. Broom, B.: Lancet 1: 899, 1960.

The author discussed the treatment of two patients with severe status asthmaticus who appeared to be dying until extreme measures were introduced to reverse their course. Each patient was given a light general anesthetic, following which an endotracheal intubation was performed and continuous intermittent positive-pressure respiration was applied. Mucus was suctioned through the endotracheal tube, and 50 mg. of trypsin dissolved in 10 c.c. of physiologic saline was extremely effective when used to lavage the upper bronchi. These procedures produced a remission of the asthma when up to 60 mg. of prednisone daily had not accomplished the same result. The rapidity with which trypsin increased the subsequent aspiration of mucus did not indicate that its action was due to proteolytic digestion. R. W.

Mold Sensitivities in Asthmatic Children. Davis, E. M.: Ann. Allergy **18**: 65, 1960.

Of 200 consecutive children in Chicago studied for bronchial asthma, 160 were sensitive to mold spores on direct skin testing. In 35 instances seasonal mold sensitivity occurred without pollen reactions. Molds tested included *Alternaria, Hormodendrum, Helminthosporium, Cephalosporium, Aspergillus flavus* or *fumigatus, Penicillium digitatum* or *rubrum, Chaetomium, Monilia sitophilia, Mucor, Fusarium, Rhizopus,* and *Phoma.* Rusts, smuts, and grain mill dust were included for certain patients. Of the 200 children studied,

180 showed positive skin-test reactions to dust, 155 to feathers, 135 to ragweed, 39 to grass, and only 6 to trees. The frequency of constitutional reactions to mold hyposensitization is noted. E. K.

Prolonged Treatment With Steroids in Severe Chronic Asthma. Phear, D., Ball, K., and Page, F.: Lancet **1**: 139, 1960.

Fifty patients with severe asthma (33 women and 17 men, with a mean age of 47 years) were studied after they had received an average of two and one-half years of cortisone therapy. These persons had been resistant to conventional therapy and were unable to work before steroid therapy was initiated. Thirty patients received oral cortisone, 50 to 75 mg. daily, while corticotrophin appeared more effective in 4 cases. Sixteen patients were treated with prednisone after it had become available. Treatment response was assessed by frequency of paroxysmal attacks, ability to work, and degree of bronchospasm.

Good results were obtained in 39 of the 50 patients, while moderate improvement was observed in 5 others. Three patients obtained no help and 3 others died during treatment. Twenty-one patients who were incapacitated prior to starting steroids were able to resume their duties, once they were on hormone therapy. Two patients developed a severe depression necessitating the discontinuance of cortisone therapy, while 3 others developed hirsuties and moonface. In 14 of these patients who were well controlled on cortisone, placebo tablets were substituted without the patient's knowledge. Within 2 months, 8 patients suffered a relapse; 2 patients required hospitalization for relief of status asthmaticus, 5 patients deteriorated more gradually, and 1 patient remained unchanged.

Another group of 11 patients with severe, chronic asthma were subjected to a double-blind study. Previous 3- to 5-month observations had suggested that these patients required maintenance doses of cortisone to keep their symptoms under control. The smallest dose of cortisone necessary, to control symptoms adequately ranged from 25 to 75 mg. daily. During the next few months the patients were gradually switched to placebo therapy, and only when a relapse had obviously occurred was cortisone restarted. Nine patients relapsed during the control period, and only one patient suffered a similar experience while on cortisone. The value of steroid therapy in the treatment of severe asthma was evident but the rapid weight gain due to an improved appetite and fluid retention made it advisable to keep most patients on a low-salt reducing diet. R. W.

MISCELLANEOUS ALLERGIES

Accidental Acquired Hypersensitivity to Tetanus Antitoxin. Sneddon, I. B.: Brit. M. J. p. 1468, May 14, 1960.

A 23-year-old woman casualty officer developed a slight swelling of her eyelids with some conjunctival congestion after she had administered tetanus antitoxin to a patient. Two days later, after giving 3 injections of tetanus antitoxin, she developed a more severe swelling of the eyelids within two to three hours. The next day she was given a test dose of 0.2 ml. of a 1:10 dilution of tetanus antitoxin, injected intracutaneously into her right forearm. Within ten minutes a wheal and flare developed locally, and within 15 minutes rhinorrhea and cough appeared. Despite administration of Adrenalin subcutaneously and an antihistamine orally, generalized urticaria, angioedema, epigastric pain, vomiting, wheezing, and dyspnea developed within two hours

after the injection. There was no evidence of vasomotor collapse. These symptoms recurred for the next two days while the patient was receiving steroids, antihistamines, and barbiturates. On the fourth day, all symptoms subsided and only a residual edema remained at the site of injection on her right forearm.

This patient gave no personal or family history of allergy, except that her father suffered from urticaria due to quinine. She had never received horse or other animal sera, therapeutically or prophylactically. Her only previous contact had occurred three years previously when she had given injections of tetanus antitoxin while she was a medical student. The patient stated that prior to the recent injections of antitoxin which she had given, she had held the syringe at eye level and expressed the material through the needle to obtain the correct doses. It was therefore considered possible that the episodes of eyelid edema which followed these administrations were caused by air-borne droplets of antitoxin reaching her conjunctivae. The mode of sensitization to antitoxin in this case remains undetermined. B. S.

Hypersensitivity to Para-Aminosalicylic Acid. Krzyski, T. K., and Young, R. C.: Canad. M. A. J. **83**: 527, 1960.

Among 894 patients who were treated over a 5-year period with para-aminosalicylic acid in doses of 6 to 12 grams daily, 33 or 3.6 per cent developed a hypersensitivity response. Skin eruption or a moderate degree of fever was the most common reaction and occurred in 21 of the patients and concomitantly in 15 patients. The rashes were urticarial, erythematous, macular, or hemorrhagic, always pruritic, and on a few occasions of a mixed type. Chills, headache, conjunctivitis, hepatotoxicity, gastrointestinal distress, cyanosis, marked drowsiness, and burning sensations in the legs were the other responses noted. Reactions developed in all age groups, from 17 months to 72 years of age. One patient received only 8 grams of medication before the reaction began, while another required 1,575 grams of PAS before the hypersensitivity reaction was noted. On the average, patients received the medication for 40 days and consumed approximately 384 grams before the allergic response developed. Sensitivity to PAS was confirmed by administering a test dose of 2 to 4 grams, which reproduced the previously described reaction. Hepatotoxicity, the only serious manifestation, occurred only after excessive daily doses were prescribed and when the medication had been continued after initial symptoms of hypersensitivity had appeared. It was stressed that PAS should be discontinued immediately after the first sign of hypersensitivity reaction. R. W.

Anaphylactoid Reaction to Ingestion of Orange. Bendersky, G., and Lupas, J. A.: J. A. M. A. **173**: 255, 1960.

A 48-year-old woman with a family history of allergy developed urticaria, angioedema, shock, and frequent premature cardiac beats about 3 hours after the ingestion of an orange. She had eaten oranges without difficulty until 2 years prior to the present reaction, at which time the ingestion of an orange was followed by a pruritic dermatitis and generalized swelling.

Intracutaneous skin tests done 24 hours after recovery from the anaphylactoid reaction were positive to freshly extracted, undiluted orange juice (obtained by needle puncture of an orange) and negative to standard stock orange extract and to diluted orange juice prepared 6 hours before testing. Scratch tests were negative to all 3 extracts. Six persons used as controls

failed to react to intracutaneous tests with the fresh orange juice. Positive passive transfer reactions were obtained with the fresh orange juice, but the stock orange extract gave negative results. H. F.

The Reproducibility of Intradermal Skin Tests: A Controlled Study. Gottlieb, P. M., Stupniker, S., and Askovitz, S. I.: Ann. Allergy **18**: 949, 1960.

A controlled study was undertaken to establish the constancy with which intradermal skin tests could be reproduced in allergic persons.

Thirty-three allergic patients who had previously shown positive skin reactions to 2 or more allergens other than house dust were tested intradermally on 2 separate occasions, with a mean interval of 6.6 months between testings. Each patient was tested in both arms with Coca's solution, histamine diphosphate (equivalent to 1:10,000 of H base), Endo-Dust 1:4,000, and oat extract, as well as 2 other selected antigens to which the subject had reacted on earlier testing. The same 6 allergens were used for the second testing. In 15 instances the placement of the second tests on the arm was inverted. In 10 instances 2 testers performed the same tests on opposite arms at the same time. The size and character of the wheals and erythema were observed and measured after 5, 10, 15, and 20 minutes. Wheals measuring less than 5×5 mm. were considered negative, those measuring 5×5 mm. to 10×10 mm. (inclusive) were considered 1+, from 10×10 mm. to 15×15 mm. were rated 2+, and so on up to 4+. The presence of pseudopods put the reaction into the 4+ category.

Tests performed with the same antigens on each arm at the same visit showed a lack of uniformity in results in 13 per cent of cases when the 5×5 mm. wheal was taken as the level of positivity, but when the 10×10 mm. wheal was used there was complete uniformity of results. When these tests were repeated after the mean interval of 6.6 months, there was a discrepancy of 27.2 per cent at the 5 mm. level but only 5.0 per cent at the 10 mm. level. Dusts, pollens, and epidermals gave more consistent results than did food extracts. When 2 different persons performed the tests simultaneously on the same patient, the results were as uniform as those obtained by a single tester. Wheaing was observed to be at its maximum between 10 and 15 minutes, which is the optimal time for reading skin tests. When the sites for testing were reversed, it was observed that the upper portion of the arm was slightly more reactive than the lower. The degree of erythema was not consistently proportional to the size of the wheal and was considered to be related to the patient's vasomotor status and skin pigmentation rather than to any immunologic response. H. F.

PHARMACOLOGY, PHYSIOLOGY, AND PATHOLOGY

Effect of Atropine on the Pulmonary Circulation During Rest and Exercise in Patients With Chronic Airway Obstruction. Williams, M. H., Zohman, L. R., and Bertrand, C. A.: Dis. Chest **37**: 597, 1960.

Twelve patients with asthma or emphysema who had been repeatedly evaluated in reference to spirometry, arterial blood gas composition, diffusing capacity of the lung during rest and exercise, and calculation of the ratio of lung dead space to tidal air were studied to determine the effect of atropine on the pulmonary circulation during rest and exercise. Right heart catheterization was performed under basal conditions with measurement of pulmonary artery or right ventricular pressure. Mean pressures were measured by electronic integration of the pressure pulses. Cardiac output was calculated, by the Fick formula, from analysis of expired gas composition and volume

and arterial and venous oxygen content. Total pulmonary resistance to blood flow, expressed as millimeters of mercury per liter per minute, was calculated by dividing the mean pulmonary artery pressure by the cardiac output. After resting measurements were obtained the patients pedaled a stationary bicycle for 5 minutes at a constant rate, and expired air and blood samples were collected during the last two minutes of exercise. The patients were permitted a recovery period during which pulmonary artery or right ventricular pressures were visually monitored until they were again at control levels. The patients were then given 0.8 mg. of atropine sulfate intravenously over a 2-minute period, and 10 minutes later the rest and exercise measurements were repeated. In 5 instances, only rest or only exercise studies were performed.

The majority of patients had less than a 20 per cent change of pulmonary resistance and showed variable and small changes of pulmonary artery pressure after the administration of atropine. Three patients showed a fair response in that their total pulmonary resistance decreased from 20 to 46 per cent during either rest or exercise, and in each instance there was some decrease in the pulmonary artery pressure. One patient had a good response with a marked decrease of total pulmonary resistance consisting of both a decrease of pulmonary artery pressure and an increase of cardiac output after the administration of atropine. The results of pulmonary function studies performed on these patients showed that, in general, those who exhibited no response to atropine gave clinical evidence of severe pulmonary emphysema, whereas the three patients who exhibited a fair response to atropine had a clinical diagnosis of bronchial asthma. The patient who showed an unequivocally good response to atropine was the only patient in the group who had recently recovered from congestive heart failure. In this patient there was no evidence of left ventricular failure, and distinction between underlying asthma or emphysema was difficult. It was postulated that when a beneficial effect is observed it is, in part, mediated by reduction of airway obstruction with reduction in the intrathoracic pressure and coincident improvement of blood flow. Thus, improved hemodynamics might be expected to follow vagal block when bronchospasm is present, whereas patients with relatively fixed airway obstruction might not be expected to show improvement.

E. W.

Pulmonary Emphysema: Report of 26 Cases Followed to Death. Carroll, D.: Bull. Johns Hopkins Hosp. **106**: 154, 1960.

Twenty-five men and 1 woman with emphysema were followed until they succumbed to their disease. The patients ranged in age from 45 to 76. Ten patients had a history of asthma or chronic bronchitis which existed for approximately 12 years prior to death, and 6 of these patients had a clinical or bronchographic diagnosis of bronchiectasis. Arterial blood, carbon dioxide and oxygen pressures, and hematocrit were determined in all cases. The blood pH and buffer base were calculated from these findings. Each patient was subjected to an average of 5 studies, the tests being carried out after approximately one-half hour's rest in the postabsorptive state. In many patients studies of arterial blood oxyhemoglobin saturation, vital capacity, maximal breathing capacity, oxygen consumption, and minute ventilation were also made.

Steroids were used in the treatment of 10 patients and appeared to benefit 4 of them. Breathing exercises were tried in 4 patients but appeared to be of no permanent help. Diamox, in general, did very little to alter the abnormal

blood gas ratios. The maximum breathing capacity usually was reduced proportionally much more than the vital capacity. Inducing myxedema in 3 patients was not beneficial and was potentially detrimental in that it tended to weaken cardiac action. Bronchospasm, pulmonary infection, and severe right heart failure were the main factors leading to severe respiratory decompensation. When the patient was in optimal cardiac and pulmonary compensation, the hypercapnia and arterial blood saturation appeared to remain rather constant. Recovery from an acute episode of respiratory decompensation did not significantly alter the serious prognosis of advanced pulmonary emphysema. Healing of infection and treatment of heart failure were the 2 most significant factors which helped to prolong the lives of these patients. R. W.

Probable Role of Blood Volume Alteration in Angioedema. Fisch, B. R., Hansen-Pruss, O. C. E., and Sieker, H. O.: Ann. Allergy **18**: 778, 1960.

Angioedema may, in some instances, be accompanied by serum loss sufficient to produce tachycardia and syncope.

A case of recurrent angioedema in a drug-sensitive person is reviewed. This patient at times developed angioedema of the typical allergic anaphylactoid type associated with bradycardia, hypotension, and syncope; on other occasions it was of the type associated with hemoconcentration, tachycardia, and syncope. The latter type failed to respond to epinephrine, norepinephrine, or steroids but did respond rapidly following the intravenous administration of fluids.

H. F.

Chest Roentgenographic Changes in Systemic Lupus Erythematosus. Bulgrin, J. G., Dubois, E. L., and Jacobson, G.: Radiology **74**: 42, 1960.

Chest roentgenograms of 207 patients with systemic lupus erythematosus were reviewed. Of these, 96 patients showed no abnormality on one or more chest roentgenograms taken over a period of several years. Autopsies were eventually performed on eight of these patients and there was no intrathoracic involvement except for strictly terminal phenomena, such as pulmonary edema or bronchopneumonia. Pleural changes, either effusions or residual thickening, occurred alone or in combination with cardiac changes in approximately 33 per cent of the patients. Rapid and unpredictable exacerbations or regressions of effusions were more frequent in patients who had combinations of pleural, cardiac, and/or pulmonary involvement than in those with pleural involvement alone. Cardiac changes which occurred alone in 25 cases or combined with pulmonary-pleural or pulmonary and pleural changes occurred in 45 patients, an incidence of cardiac involvement in all of 35 per cent of the patients. These changes in the heart consisted of nondistinctive enlargement of minimal to moderate degree. Rapid changes in heart size were more frequent where cardiac disease was combined with some other intrathoracic abnormality than when cardiac enlargement was an isolated finding. Except for three cases in which pericardial effusion alone accounted for the enlarged heart, multiple and inseparable causes of cardiomegaly were present. These included pericardial thickening or adhesions, endocarditis, myocarditis, and such contributory factors as hypertension, renal disease, and anemia. Pulmonary changes occurred in 26 (12.6 per cent) of the patients. Of these, 5 showed infiltrations not related to systemic lupus erythematosus in any manner. There were five cases of pulmonary edema, of which 2 were terminal, one was unrelated to other pulmonary changes, and two were associated on one occasion with rapidly resolving pneumonia. Pneumonia resolving promptly as a single event occurred

in 7 patients and had an entirely nonspecific appearance. The pneumonia resolved promptly but resumed in 4 patients. Nonspecific localized infiltrations of unknown duration were seen in two patients who were lost to follow-up. Of the other three patients with pulmonary infiltrations, one had extensive infiltration in the right upper and left lower lobes which persisted over a 4-month period and showed progression. At autopsy, this patient's alveoli were filled with a protein exudate, numerous areas of round-cell and polymorphonuclear infiltration and thickening of some septa with round-cell infiltrations. Many vessels showed thickening of the walls with wavy strands of collagenous-fibrous material. There were areas of atelectasis and fibrosis. The second patient's roentgenogram showed an extensive bilateral infiltration that had the distribution of pulmonary edema which became steadily more extensive but which responded to steroid therapy. In the third patient, a number of spherical lesions developed, one of which showed cavitation. These persisted for one month and then gradually diminished. This patient died after disappearance of the nodular infiltrations and, at autopsy, was found to have miliary cryptococcosis. It was concluded that because of the protean manifestations of systemic lupus erythematosus, variations in clinical material from series to series, differences in roentgen coverage, and perhaps other factors have resulted in such extreme variability in the reported incidence of roentgenographic changes in the chest. One must beware of drawing conclusions on the basis of any single study. E. W.

Effect of Certain Tranquilizers on the Reticulo-Endothelial System. Vinegar, R., and Berger, F. M.: Proc. Soc. Exper. Biol. & Med. **102**: 88, 1959.

Excessive doses of certain tranquilizer drugs given to mice decrease the phagocytic activity of the reticulo-endothelial system as measured by determining the blood clearance of intravenously administered carbon particles in the form of India ink. Groups of male CF 1 mice were pretreated with various tranquilizing drug preparations and saline solution as a control. Following drug therapy, India ink of known particle size was injected intravenously. The blood carbon particle concentration was determined spectrophotometrically 8, 15, and 22 minutes after ink injection.

Large doses of chlorpromazine, hydroxyzine, and reserpine were required to delay the rate of particle clearance. Phenylglycadol caused only a slight delay at comparably lower doses, while meprobamate had no effect on clearance. Hydroxyzine, the only drug that was nonlethal when administered in high dosage to adrenalectomized mice, did not cause a delay in clearing of particles from the blood in these animals. The authors feel that depression of the reticulo-endothelial system caused by large doses of the above tranquilizers is mediated by a stimulant effect on secretion of adrenal corticoids. D. S.

Cardiovascular and Respiratory Effects of Lethal Doses of Histamine and Compound 48/80 in Rabbits. Papacostas, C. A., and Loew, E. R.: Proc. Soc. Exper. Biol. & Med. **100**: 604, 1959.

Lethal doses of Compound 48/80, a potent liberator of endogenous histamine in several species, were administered to groups of albino rabbits which could be kept alive as long as artificial respiration was administered. Blood pressure changes appeared to be dependent on respiratory effects, since normal pressure was maintained with artificial respiration. Normal ECG tracings were obtained in the artificially respirated animal. In another group of rabbits injected with a lethal dose of histamine, the blood pressure fell to zero and death ensued despite immediate administration of artificial respiration. Marked ECG abnormalities were noted in these animals. In view of the very rapid onset of

blood pressure and cardiac changes and the failure of artificial respiration as a resuscitating measure, the primary effect of histamine appeared to be cardiovascular. Respiration effects were probably secondary to this main action. The lethal action of Compound 48/80 in rabbits apparently is not mediated by release of endogenous histamine, since large doses do not produce histamine-like effects. H. PELZ

Effects of Compound 48/80 on Toxicity of Histamine and of Serotonin in Mice. Higginbotham, R. D.: Proc. Soc. Exper. Biol. & Med. **102**: 4, 1959.

The authors studied the relative importance of tissue mast-cell constituents, histamine, serotonin, and heparin in the production of lethal intoxication in mice by Compound 48/80, a synthetic alkylamine which causes mast-cell degranulation. When the amounts of several sublethal doses of Compound 48/80 were plotted against the amount of amine needed to produce an LD_{50} in groups of mice it was found that Compound 48/80 had an additive effect on histamine and a synergistic effect on serotonin toxicity. It was also noted that this additive or synergistic effect of Compound 48/80 with injected amine could not be directly attributed to the supplementation of exogenously administered amines by those released from the tissues but was due to a primary toxic effect of this agent on the tissues. Heparin was found to exert a protective effect against the lethal action of a Compound 48/80-amine combination. The amount of heparin required for protection against any given dose of Compound 48/80 depended on the amount of histamine or serotonin injected along with the degranulating substance. Since there is insufficient tissue histamine or serotonin present to account for the lethal effects of Compound 48/80, this drug must possess a primary lethal effect independent of its ability to cause release of amines from mast cells.

The authors feel that heparin interferes with the action of Compound 48/80 by an ion exchange of this compound for histamine, or serotonin within the tissue mast cell. The subsequent release of these amines is, then, an indication of this ion exchange reaction rather than a sign of toxicity. D. S.

Demonstration of Gamma Globulin in Vascular Lesions of Experimental Necrotizing Arteritis in Rats. Goroku, O., Cohen, S., Singer, E. J., Rosenfield, R., and Strauss, L.: Proc. Soc. Exper. Biol. & Med. **102**: 187, 1959.

The presence of gamma globulin in the walls of blood vessels damaged by necrotizing arteritis (not due to antigen-antibody reaction) was demonstrated by the fluorescent antibody technique of Coons.

Three groups of female Sprague Dawley rats were unilaterally nephrectomized. Group I subsequently received 1.5 mg. DOCA 3 times a week for 5 weeks, after which a daily dose of 2 to 5 mg. was given for varying periods up to 7½ months prior to sacrifice. Group 2 was treated similarly, but the animals were sacrificed within the first 5 weeks. In addition to a standard diet, both groups drank 1 per cent saline solution. Group 3 received no postoperative treatment and drank tap water. Following sacrifice, tissues were treated by formalin fixation and embedding in paraffin as well as by the snap-freeze method. Fluorescein-labelled antibody for staining tissue specimens was obtained by conjugating fluorescein-isothiocyanate with gamma globulin from rabbits immunized with rat gamma globulin (RGG). Controls consisted of (1) testing the system with nonlabelled rabbit anti-RGG serum for blocking of the reaction and (2) testing with normal rabbit serum for failure to block the reaction.

Animals in Groups 2 and 3 showed no vascular lesions. Fluorescence was noted in the muscular layers of splanchnic arteries of animals in Group 1, as well as in renal glomerular capillaries and in the cells of Bowman's capsule. Control studies with labelled anti-RGG serum from which anti-RGG had been removed by precipitation yielded no specific fluorescence in necrotic vessel walls.

These experiments suggest a selective deposition of RGG in damaged splanchnic vessel walls rather than a random deposition by diffusion of gamma globulin from circulating blood. Antibody may not be required for this to occur. D. S.

IMMUNOLOGY

Studies in Immunization. I. The Effect of Route of Injection of Bovine Serum Albumin in Freund Adjuvant on Production of Circulating Antibody and Delayed Hypersensitivity. Leskowitz, S., and Waksman, B. H.: J. Immunol. **84**: 58, 1960.

Rabbits were given a single "high" dose consisting of 25 mg. of bovine serum albumin (BSA) or a "low" dose of 2.5 mg. in adjuvant mixtures containing dead tubercle bacilli. The total volume injected was 0.4 ml., given by one of the following routes: intramuscular, 0.1 ml. in four sites; intraperitoneal, 0.2 ml. in two sites; intracutaneous, 0.1 ml. in four sites; foot pad, 0.1 ml. in four toes; subcutaneous, 0.1 ml. in four sites; intravenous, in 9 ml. of saline solution.

Frequent blood samples were taken at intervals over a period of 14 to 18 weeks for antibody studies. Then each animal received a "booster" dose of 10 mg. of BSA in saline solution intravenously. After each bleeding, the animal was tested by an intracutaneous injection of BSA (10, 1, and 0.1 μg N in 0.1 ml.) and an intracorneal injection (2 μg N in 0.02 ml.). Readings were taken at 4 to 6 hours and at 24, 48, and 72 hours. The level of delayed hypersensitiveness at any time was estimated by combining the skin and corneal reaction readings, the latter being considered the more important of the two.

Early antibody production was most apparent with the intracutaneous and foot pad methods, where maximal levels were reached in 2 to 4 weeks. Intraperitoneal, intramuscular, and subcutaneous injections produced slower but more prolonged rises in antibody production. The highest titers followed intramuscular and subcutaneous injections. The lowest were obtained by the intracutaneous route, and these tended to fall off after 4 weeks. All other titers were well maintained during the period of observation, except those of the intravenous method which proved to be the least effective antibody producer of all. The antibody responses to a booster injection bore no relation to previously attained antibody levels. The high and low antigen dose groups differed very little in antibody titers.

Delayed sensitivity, as judged by averages of the skin and corneal reactions, also showed a correlation to the route of antigenic administration. Intracutaneous and foot pad inoculation produced an intense delayed sensitization within 6 or 7 days; this reached a maximum in 2 or 3 weeks and was sustained for the period of observation. Intramuscular and intraperitoneal injections produced delayed sensitivity which was slower in starting and in reaching a peak but which was well sustained. The intravenous method was ineffective for producing delayed sensitization. The "booster" doses of antigen were followed by a pronounced reduction of delayed sensitivity. B. S.

Factors Affecting the Suppression of Allergic Encephalomyelitis by Homologous Brain Protein Fractions. Kies, M. W., Shaw, C-M, Fahlberg, W. J., and Alvord, E. C., Jr.: Ann. Allergy **18**: 849, 1960.

In the course of studying skin reactivity to variously prepared fractions of neural tissue in sensitized animals, it was discovered that repeated skin testing with a purified guinea pig brain protein fraction enhanced the development of experimental allergic encephalomyelitis (EAE).

Guinea pigs were injected with adjuvant and various neural tissue preparations. On the eighth, thirteenth, and eighteenth days after sensitization, intracutaneous or intravenous injections of antigen were administered. Clinical manifestations of encephalomyelitis were suppressed in animals treated in the interval after the sensitizing injection with whole brain material. Histologic changes, however, were equally prevalent in both treated and untreated animals. When large amounts of antigen were given initially to induce the disease, or when doses of suppressive antigen were reduced to one-fifth of a known effective dose, there was no suppression of clinical disease. A water-soluble fraction incapable of eliciting encephalitis was ineffective in suppressing encephalitis.

Encephalitis developed between the tenth and the twenty-first days after immunization in the control group. Treated animals observed for 45 days failed to develop clinical encephalitis, although they showed histologic damage. Clinical suppression of encephalitis could be achieved with guinea pig protein in animals immunized with bovine spinal cord, indicating that the reaction was not species specific. Intravenous or intracutaneous administration of suppressive doses was equally effective. It is suggested that the suppressive doses act by providing an antigen excess which "neutralizes any preformed antibody and/or suppresses its formation. Thus exposure of the brain to the hypothetically harmful effects of the antibody is prevented." E. K.

In Vitro Passive Transfer of Atopic Hypersensitivity. Middleton, E., Jr.: Proc. Soc. Exper. Biol. & Med. **104**: 245, 1960.

The purpose of these experiments was to demonstrate in vitro passive sensitization of nonallergic human leukocytes with plasma from ragweed-sensitive subjects. Increased histamine release in the presence of ragweed antigen was considered to be an indication of passive sensitization. To heparinized normal whole blood was added sensitive plasma, unaltered or in dilution, or plasma from sensitive whole blood previously treated with ragweed. After incubation at 37° C. for two hours, ragweed extract was added, and the mixture was incubated for 30 minutes. The tubes were then centrifuged and the plasma was analyzed for its histamine content. In pairing the products of the donor and "acceptor," matches were made according to major blood groups. In 10 attempts with 6 sensitive plasmas and 7 normal bloods, 3 pairs of individuals provided systems which showed histamine release in the presence of ragweed antigen. Blood grouping did not prove to be a factor in the results. Dilution of sensitive plasma resulted in a diminution of the histamine release. Previous treatment of the sensitive plasma with ragweed diminished the capacity of the normal cells, sensitized with such plasma, to release histamine. The more ragweed that was used in such preliminary treatment, the less histamine was released in the final test. A sensitive plasma did not sensitize every "acceptor." The cells of an acceptor responsive to one plasma failed to react with other sensitive plasmas. B. S.

The Chemistry of Allergens. XIV. Effect of Heat and pH on the Precipitin Reaction and Reagin Neutralizing Capacity of the Castor Bean Allergen, CB-IC. Spies, J. R., Coulson, E. J., Bernton, H. S., Stevens, H., and Strauss, A. A.: Ann. Allergy **18**: 393, 1960.

Castor bean fraction CB-IC is a polysaccharide protein which is stable in boiling water. This fraction was heated at 100°, 115°, and 130° C. in buffered solutions at various pH values in sealed tubes. Precipitating capacity for rabbit antiserum and capacity to neutralize reagin antibody were lost most quickly in alkaline solution. Doubtful precipitin reactions were obtained over a considerable period of time before total destruction was obtained. Also, positive passive-transfer tests were elicited "even when the reagin neutralizing capacities were reduced to less than 0.026 per cent." E. K.

The Tuberculin Test and the Diagnosis of Clinical Tuberculosis. Johnston, W. W., Saltzman, H. A., Bufkin, J. H., and Smith, D. T.: Am. Rev. Res. Dis. **81**: 189, 1960.

Among 81 patients with proved tuberculosis, 84 per cent had reactions to first-strength PPD (1 TU), 94 per cent to intermediate-strength PPD (5 TU), 6 per cent failed to react to 5 TU, and one was a nonreactor to second-strength PPD. In another series of 120 patients who were diagnosed as tuberculous, 69 per cent reacted to a 1:1,000 (or more dilute) solution of OT, and 15 per cent failed to react to the 1:100 strength of OT. A group of 8 medical students who gave negative reactions to 0.005 mg. of PPD had not the slightest reaction to 0.01 mg. of PPD. Six of the students tested with ten times the second-strength PPD (0.05 mg.) showed a chemical irritation reaction which was marked in 6 hours, reached its maximum before 24 hours, and had practically disappeared in 48 hours. The authors conclude from this that reactions to 1 mg. of OT or to second-strength PPD (0.005 mg.) are true allergic reactions and are not the result of chemical irritation from tuberculin. The skin reaction does not distinguish allergy to an atypical acid-fast organism from that to a true tubercle bacillus. "A negative reaction to 1 mg. of OT or 0.005 mg. of PPD by patients who are in reasonably good physical condition almost eliminates the possibility of infection with either atypical acid-fast organisms or human tubercle bacilli." "Healthy subjects reacting only to second-strength PPD (0.005) are more resistant to the development of clinical tuberculosis than those who react strongly to 5 TU and those who fail to react at all to second-strength PPD." The percentage of patients with clinical tuberculosis who fail to react positively to intermediate doses of tuberculin (5 TU) varied from a low of 0.4 per cent in one state sanatorium to 8.7 per cent in a different sanatorium and to 31 per cent in a general hospital. E. W.

Intermediate-Strength Purified Protein Derivative: Its Diagnostic Significance in Active Tuberculosis. Katz, S., Duvall, R. C., Ryan, T. J., O'Connor, T. F., Marilly, R. J., and Perry, R. B.: Am. Rev. Resp. Dis. **81**: 196, 1960.

Recent reports have "convincingly shown that the second-strength purified protein derivative (PPD) skin test has limited value because fully 33 per cent of the population will give non-specific reactions." Thus, the validity of testing with intermediate-strength PPD becomes important. Four-hundred sixteen patients with proven tuberculosis were skin-tested with PPD (0.0001 mg.) of intermediate strength. Of these patients, 92.8 per cent gave positive reactions the first time they were studied. When the same intermediate dose was reapplied, only 1.7 per cent of the total did not give a positive reaction. The 7 patients who had negative reactions were analyzed for the cause of anergy. It was found that 3 patients were moribund with far-advanced tuberculous disease.

One patient with moderately advanced tuberculous disease was extremely toxic from a gangrenous extremity at the time of the skin tests. Another patient had miliary tuberculosis and was receiving steroid therapy. These 5 patients were over 65 years of age. Another patient had proved sarcoidosis and then developed tuberculosis; her skin reactions were negative while she was receiving intermittent steroid therapy. In only one patient was there no obvious or striking cause for anergy. Although he had a small skin reaction, it did not fit the criteria as outlined by the authors. It was concluded that the true significance of the intermediate dose of PPD lies in the fact that it is 99.76 per cent accurate, with a false negative incidence of only 0.24 per cent, if the skin reaction is restudied in all of the patients with initially negative or doubtful reactions and if patients with obvious cause for anergy are excluded. E. W.

Studies on Tuberculin Fever. I. The Mechanism of Fever in Tuberculin Hypersensitivity. Hall, C. H., Jr., and Atkins, E.: J. Exper. Med. **109**: 339, 1959.

To determine whether febrile response to old tuberculin (O.T.) is a hypersensitive reaction or due to contaminating endotoxins, rabbits were immunized with BCG vaccine and challenged with O.T. intravenously. Tuberculin-sensitive animals developed febrile responses to O.T., whereas normal controls and animals rendered pyrogen resistant by repeated typhoid injections were not affected by O.T., even in very large doses. Certain lots of O.T., however, proved to be pyrogenic for normal animals. Febrile response did not correlate with the size of the tuberculin skin reaction. The febrile responses to typhoid vaccine in normal and tuberculin-sensitive animals were alike and proportional to the number of organisms used, indicating that tuberculin-sensitive animals are not more than normally reactive to endotoxins.

Repeated daily intravenous injections of O.T. reduced or abolished febrile response to O.T., the effect being definite by the fifth day. Tolerance to tuberculin, however, unlike tolerance to endotoxin, was not altered by incubation of O.T. with serum in vitro or affected by the administration of Thorotrast. Cross tolerance between endotoxins and tuberculin was absent. A circulating pyrogen, transferable to normal animals, was present in the sera of O.T.-challenged, tuberculin-sensitive animals. Its titer was proportional to the degree of fever induced. "It is postulated that tuberculin fever is due to a circulating endogenous pyrogen released by a specific action of O.T. on sensitized cells of the host." E. K.

Studies on the Adjunct Action of Bacterial Endotoxin on Antibody Formation. III. Histologic Response of the Rabbit Spleen to a Single Injection of a Purified Protein Antigen. Ward, P. A., Johnson, A. G., and Abell, M. R.: J. Exper. Med. **109**: 463, 1959.

A single dose of bovine gamma globulin was injected intravenously, alone or in combination with endotoxin from *E. coli*, into groups of rabbits. Animals were sacrificed at intervals of from 1 to 18 days. Endotoxin accelerated and intensified the antibody response. Circulatory antibody was present on the fourth day in endotoxin-treated animals, as compared to the eighth day in the controls. Antibody to the endotoxin itself was noted in only one rabbit, and then in low (1:20) titer. Histologic study seemed to indicate that a modified reticular cell in the spleen was the important cell in antibody formation. This cell may represent a large blast cell of the lymphocyte series. It acquired a ribonucleic acid staining property, indicating active protein synthesis (pyroninophilic property). Active mitosis of this cell was observed at the time of onset of antibody formation. When hemagglutinin titers were at their peak,

mitotic activity, cell differentiation, and enlargement of splenic follicles were also maximal. This was followed by a phase of reduction. After several days these cells disappear and are replaced by normal medium-sized lymphocytes in the follicles. Such histologic sequences were not found in animals given only endotoxin. In these animals no new cellular types appeared, plasma cells were observed, and only minimal changes were found in the red pulp. It is suggested that plasma cells may arise only after secondary or intense antigenic stimulation. E. K.

Delayed Hypersensitivity in the Development of Circulating Antibody. The Effect of X-irradiation. Salvin, S. B., and Smith, R. F.: J. Exper. Med. **109**: 325, 1959.

Total body irradiation of guinea pigs in varying doses up to 300 r (lethal to 50 per cent of the animals), either 18 hours prior to injection of antigen or immediately prior to sensitization, failed to inhibit the induction of delayed hypersensitivity to purified diphtheria toxoid. Both delayed cutaneous responses and Arthus reactions were elicited. Irradiated animals exhibited a more prolonged period in which delayed reactions could be demonstrated, although circulating antibody was inhibited in proportion to the amount of irradiation. Arthus responses were noted in control animals on the eleventh to thirteenth days. In irradiated animals Arthus reactions of equal intensity could be elicited, but they appeared only after the nineteenth day. From the eleventh to the fifteenth days, when leukocyte counts were lowest, some irradiated animals had either subnormal or no delayed reactions, although moderately reduced lymphocyte counts did not markedly influence the hypersensitivity reaction.

Lymph node cells from irradiated sensitized guinea pigs induced hypersensitivity in normal recipients in characteristic fashion, despite the absence ($<$ .001 units antitoxin/1 ml.) of circulating antibody at the time. Irradiation 18 or more hours after administration of the intracutaneous sensitizing antigen failed to extend the period of delayed reaction or the time of appearance of the Arthus reactions. Circulating antibody titers were lower in these irradiated animals. Transfusions of leukocytes or normal serum (including complement) into irradiated animals "had no apparent effect on reducing the damage of x-ray to whatever regulates the rate of antibody synthesis." It is suggested that the immune response may be initiated by a process which determines rate of antibody development. This initial phase lasts only a few hours and is radiosensitive. There follows a stage of delayed hypersensitivity which, in turn, precedes the development of a globulin-antibody-forming mechanism or cell.

E. K.

The In Vitro Sensitivity of Leukocytes From Allergic and Non-Allergic Subjects to the Products of Growth of Microorganisms. Hall, H. F., Scherago, M., Kaufman, M., and Mayer, L. D.: Ann. Allergy **18**: 401, 1960.

Leukocytes from apparently healthy college students were compared with leukocytes from patients having frank atopy. Testing was done by an in vitro leukocyte migration technique, with broth filtrates of 14 microorganisms chosen for common occurrence, to determine the cytotoxic index. Leukocytes from the clinically allergic subjects showed a greater frequency of sensitivity to bacterial filtrates and had a higher incidence of sensitivity to multiple bacterial filtrates than leukocytes from the students. The most striking difference was seen with the organism *N. catarrhalis* to which 2 of 27 students and 8 of 13 clinically allergic persons reacted. E. K.

OTORHINOLOGY AND OPHTHALMOLOGY

A Study of the Nasal Cytology in Infants With Eczemoid Dermatitis. Crawford, L. V.: Ann. Allergy **18**: 59, 1960

Infants with eczematoid dermatitis, ranging in age from 5 to 24 months, were subjected on 3 occasions to nasal smear tests for eosinophils. Those manifesting respiratory tract allergy were excluded. Of 50 infants with atopic eczema, 26 (52 per cent) showed either clumps of eosinophils or over 10 per cent eosinophils in one of the 3 specimens. Two of 20 infants classified as having seborrheic eczema showed nasal eosinophilia. One of 15 infants with contact dermatitis and 2 of 50 control children had eosinophils in their nasal secretions.

Among a series of 50 newborn infants in the hospital nursery, 13 (26 per cent) showed nasal esoinophilia.

The eczematous children were followed for 2 years, during which time 62 per cent of the atopic eczema group developed respiratory allergy. Of the 26 atopic children who previously showed nasal eosinophilia, 22 (85 per cent) developed respiratory allergy. Of the 9 infants with atopic eczema who had previously had negative nasal smears, only 37 per cent progressed to allergic rhinitis or asthma. One control infant developed respiratory allergic disease despite his earlier negative nasal smear. "Our studies would suggest that the eosinophil is attracted to the respiratory shock organ often before the antigen antibody reaction is of a severe enough degree to be recognized clinically.

E. K.

ANAPHYLAXIS

Biologic Reactivity of Antigen and Antibody in Specific Precipitate. Rosenberg, L. T., Chandler, M. H., and Fischel, E. E.: Proc. Soc. Exper. Biol. & Med. **100**: 649, 1959.

The capacity of antigen and antibody in washed precipitate to sensitize the guinea pig was investigated. Guinea pigs injected intravenously with the specific precipitate showed signs of anaphylaxis when challenged with specific antigen 5 to 72 hours later, thus indicating that sufficient antibody is present in the precipitate to produce sensitization. Passive cutaneous anaphylaxis can be elicited by the intravenous injection of the complex, thus demonstrating the capacity of the specific precipitate to act as an antigenic challenge. In both modes of anaphylaxis, the uncombined antibody and the uncombined antigen elicited greater reactions in a shorter period of time than the specific complex. This ability of the specific precipitate to retain the specific biologic reactivity of both antigen and antibody is attributed to unsaturation of the combining sites as well as to some dissociation of the complex in vivo.

H. Pelz

MISCELLANEOUS

Pulmonary and Allergic Manifestations of Cystic Fibrosis of the Pancreas. Fisher, A. M., VanMetre, T. E., and Winkenwerder, W. L.: Am. J. M. Sc. **239**: 430, 1960.

Cystic fibrosis of the pancreas (mucoviscidosis) has commonly been associated with bronchial asthma, but only recently has it become apparent that the condition may also be associated with other atopic conditions, such as hay

fever, rhinitis, and nasal polyps. These conditions have been observed in patients who have survived the pulmonary infections frequently complicating cystic fibrosis in early childhood. Although the asthma in cystic fibrosis is primarily believed to be the result of the thick mucous secretions found in the bronchopulmonary tree, complicating atopic sensitivities were demonstrated by positive skin-test reactions to pollens, inhalants, foods, and bacteria in 6 of 14 patients with cystic fibrosis. Two other patients on whom skin tests were not done had asthma or rhinitis and nasal polyps.

The most important diagnostic features of the disease are an elevation of the sodium and chloride content of the sweat and a lowering of the pancreatic enzymes in the duodenum. Treatment of the condition is mainly symptomatic and includes the administration of bronchodilators, pancreatic enzymes, all the fat-soluble vitamins, antibiotics, corticosteroids, and antiallergic management. Two cases of cystic fibrosis observed in young adults and associated with atopy are reported.

H. F.

A Survey of the Serum Protein Electrophoresis Pattern in Allergic Children. Dees, S. C., and Grunt, J. A.: Ann. Allergy **18**: 50, 1960.

A series of 283 consecutive allergic children, ranging in age from 4 months to 14 years, were studied at the time of their initial allergic survey for electrophoretic serum protein pattern. The distribution of serum components was comparable to that for normal children. There was no characteristic difference in serum patterns among the various diseases, such as rhinitis, asthma, or eczema. Isoagglutinin titers have been suggested as a screening device to select persons likely to have low gamma globulin levels. Isoagglutinin titers below 1:32 were unrelated to low serum protein levels. In this series, although boys outnumbered girls (especially in the first year and in the 3- to 5-year age group), there was no sex difference in the serum protein fractions at any age. The presence of secondary infection did not alter the protein pattern. Study of blood types of these children failed to confirm reports that allergic children tend to a particular blood group type.

E. K.

ANNOUNCEMENT

Allergy Abstracts has been published since 1936 by members of the Allergy Division of The Jewish Hospital of Brooklyn. The Editorial Board is comprised of former residents of this department who contribute their services.

Allergy Abstracts selects and abstracts those articles in the literature which may be of clinical or theoretical interest to workers in the field of allergy. Each abstract represents a summary of the author's findings and views, and its inclusion in Allergy Abstracts does not imply approval of its contents by the editor.—*The Editors.*